

## Supplemental Material

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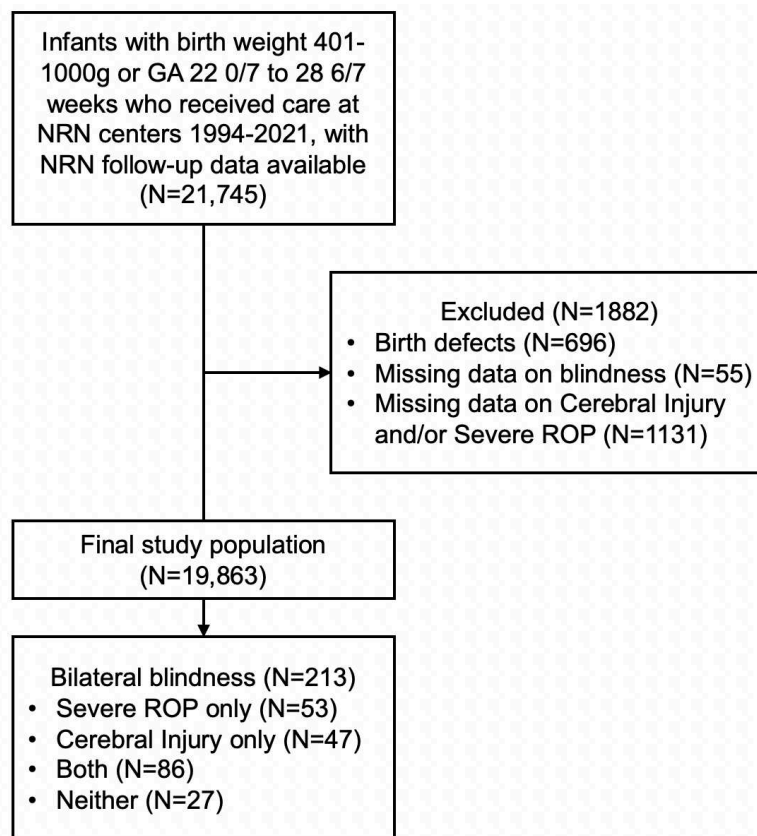
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This supplementary material has been provided by the authors to give readers additional information about their work.



### eFigure 1. Participant Flow Diagram

21,745 infants who received care at NRN centers fulfilled eligibility criteria in terms of birth weight or gestational age, as well as sufficient follow-up data on visual outcomes. There were 1882 infants excluded from the study due to genetic syndromes, congenital neurological malformations, or ocular malformations, or missing data on the outcome or exposures. This resulted in a final study population of 19,863.

Abbreviations: GA, Gestational Age; NRN, Neonatal Research Network; ROP, Retinopathy of Prematurity.

**eTable 1. Characteristics of Surviving Children Born at 22 0/7 to 28 6/7 Weeks' Gestational Age Excluded due to Missing Data versus Included in Analysis**

	Excluded due to missing data N=1,186	Included in analysis N=19,863
Maternal age — yr	N=1185 27.3 ± 6.6	N=19859 27.7 ± 6.6
Race — no./total no. (%) <sup>a,b</sup>	N=1175	N=19586
Black	453 (39%)	8479 (43%)
White	675 (57%)	10208 (52%)
Other	47 (4.0%)	899 (4.6%)
Hispanic or Latino ethnic group — no./total no. (%) <sup>a,b</sup>	N=1166 154 (13%)	N=19411 3197 (16%)
Mother's education — no./total no. (%)	N=1186	N=19863
Less than high school diploma	289 (24%)	4640 (23%)
High school diploma	359 (30%)	5809 (29%)
Partial college/trade/technical	253 (21%)	4717 (24%)
College degree or more	253 (21%)	4321 (22%)
Unknown	32 (2.7%)	376 (1.9%)
Received any antenatal glucocorticoids — no./total no. (%) <sup>b</sup>	N=1181 928 (79%)	N=19811 16829 (85%)
Public maternal medical insurance — no./total no. (%) <sup>b</sup>	N=1184 629 (53%)	N=19856 11329 (57%)
Prenatal care — no./total no. (%)	N=1182 1102 (93%)	N=19840 18755 (95%)
Diabetes prior to pregnancy (2016+) — no./total no. (%)	N=91 2 (2.2%)	N=3354 149 (4.4%)
Insulin-dependent diabetes — no./total no. (%)	N=1182 42 (3.6%)	N=19793 768 (3.9%)
Gestational diabetes mellitus (2016+) — no./total no. (%)	N=90 4 (4.4%)	N=3322 157 (4.7%)
Maternal hypertension — no./total no. (%) <sup>b</sup>	N=1182 391 (33%)	N=19826 5240 (26%)
Chorioamnionitis (2006+) — no./total no. (%) <sup>c</sup>	N=226 30 (13%)	N=10346 1718 (17%)
Histologic chorioamnionitis (2006+) — no./total no. (%)	N=203 96 (47%)	N=9150 4941 (54%)
Antenatal antibiotic exposure — no./total no. (%) <sup>b</sup>	N=1177 702 (60%)	N=19753 14124 (72%)
Magnesium sulfate exposure (2011+) — no./total no. (%)	N=163 134 (82%)	N=6869 5635 (82%)
Mode of delivery — no./total no. (%)	N=1185	N=19835
Vaginal vertex	346 (29%)	6141 (31%)
Vaginal breech	47 (4.0%)	889 (4.5%)
C-section	792 (67%)	12805 (65%)
Birth weight — g <sup>d</sup>	N=1186 840 ± 142	N=19863 782 ± 158
Gestational age — wk <sup>d</sup>	N=1185 26.9 ± 2.4	N=19861 25.6 ± 1.7
Sex — no (%)	N=1185	N=19860
Male sex	541 (46%)	9647 (49%)
Female sex	642 (54%)	10201 (51%)
Ambiguous sex	2 (0.2%)	12 (0.1%)

	<b>Excluded due to missing data N=1,186</b>	<b>Included in analysis N=19,863</b>
Small for gestational age — no. (%) <sup>d</sup>	N=1184 284 (24%)	N=19857 2234 (11%)
Multiple birth — no. (%)	N=1186 261 (22%)	N=19863 4709 (24%)
Median 5-min Apgar score (5th to 95th percentile) <sup>b</sup>	N=1174 7 (6-8)	N=19708 7 (6-8)
5-min Apgar score ≤5 — no./total no. (%) <sup>d</sup>	N=1174 200 (17%)	N=19708 4846 (25%)

The middle column is comprised of 55 infants missing information on blindness and 1131 missing information on cerebral injury and/or severe ROP. Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

<sup>a</sup> Race and ethnic group were reported by the parent or guardian. "Other" includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or more than one race.

<sup>b</sup> Significant at  $p < 0.01$  (Chi-square, Wilcoxon, or Median test).

<sup>c</sup> Chorioamnionitis as documented in the mother's medical record.

No characteristics were significant only at  $p < 0.05$  (Chi-square or Wilcoxon test).

Missing data: Maternal age=5, Race=288, Hispanic or Latino ethnic group=472, Mother's education=408 (Unknown), Antenatal glucocorticoids=57, Gestational age=3, Sex=4, 5-min Apgar score=167, SGA=8, Public maternal medical insurance=9, Prenatal care=27, Diabetes prior to pregnancy=17604, Insulin-dependent diabetes=74, Gestational Diabetes Mellitus=17637, Hypertension=41, Chorioamnionitis=10477, Histologic chorioamnionitis=11696, Antenatal antibiotic exposure=119, Mg sulfate exposure=14017, Mode of delivery=29.

**eTable 2. Study Population by Gestational Age**

Gestational Age	N	%
19 weeks	1	0.0%
20 weeks	2	0.0%
21 weeks	6	0.0%
22 weeks	184	0.9%
23 weeks	1347	6.8%
24 weeks	3484	18%
25 weeks	4720	24%
26 weeks	5273	27%
27 weeks	2357	12%
28 weeks	1437	7.2%
29 weeks	514	2.6%
30 weeks	296	1.5%
31 weeks	132	0.7%
32 weeks	75	0.4%
33 weeks	18	0.1%
34 weeks	11	0.1%
35 weeks	4	0.0%
Total	19,861 <sup>a</sup>	100%

<sup>a</sup> 2 infants are missing gestational age.

**eTable 3. Study Population by Birthweight, 100g Increments**

Birthweight	N	%
300 – 399g	30	0.2%
400 – 499g	529	2.7%
500 – 599g	1905	9.6%
600 – 699g	3766	19%
700 – 799g	4362	22%
800 – 899g	4291	22%
900 – 999g	3719	19%
1000 – 1099g	795	4.0%
1100 – 1199g	283	1.4%
1200 – 1299g	128	0.6%
1300 – 1399g	41	0.2%
1400 – 1499g	9	0.0%
1500 – 1599g	2	0.0%
1600 – 1699g	2	0.0%
1700 – 1799g	1	0.0%
Total	19,863	100%

**eTable 4. Risk Differences for Blindness**

Risk Factor	RD <sup>a</sup> (95% CI)	p-value
Cerebral Injury	1.4% (0.9-1.8%)	<0.001
Severe ROP	1.4% (0.8-2.0%)	<0.001
Additive Interaction	2.9% (1.2-4.5%)	<0.001

Abbreviation: ROP, Retinopathy of Prematurity.

<sup>a</sup> The Risk Differences and p-values are from a linear regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the additive interaction between cerebral injury and severe ROP, and center as a cluster effect.

**eTable 5. Adjusted Odds Ratios (aOR) and 95% Confidence Interval for Blindness Before and Since 2006**

Risk Factor	1994-2005 births (N=9483)		2006-2021 births (N=10,380)	
	aOR <sup>a</sup> (95% CI)	p-value	aOR <sup>a</sup> (95% CI)	p-value
Cerebral Injury, with Severe ROP present	1.98 (1.12-3.51)	0.02	5.90 (3.67-9.47)	<0.0001
Cerebral Injury, with Severe ROP absent	5.00 (2.50-9.97)	<0.0001	10.7 (5.69-20.1)	<0.0001
Severe ROP, with Cerebral Injury present	4.06 (1.80-9.14)	0.0007	3.39 (2.21-5.20)	<0.0001
Severe ROP, with Cerebral Injury absent	10.2 (4.70-22.2)	<0.0001	6.15 (3.47-10.9)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.11	--	0.07
Both Cerebral Injury and Severe ROP vs. Neither <sup>b</sup>	20.3 (8.42-48.8)	<0.0001	36.3 (17.6-74.8)	<0.0001

Abbreviation: ROP, Retinopathy of Prematurity.

<sup>a</sup> The adjusted odds ratios and p-values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, and center as a cluster effect. Additionally, the following variables were removed during backward stepwise selection: maternal public insurance, gestational age, birth year, antenatal steroids, Hispanic ethnicity, maternal hypertension, and maternal insulin-dependent diabetes.

<sup>b</sup> The adjusted odds ratio and p-value for Both cerebral injury and severe ROP vs. Neither is from the same logistic regression model but using different reference levels for the two risk factors, assessing Cerebral injury and Severe ROP as a 4-level variable (Cerebral injury only, Severe ROP only, Both, Neither) with no interaction term.

**eTable 6. Adjusted Odds Ratios (aOR) and 95% Confidence Interval for Blindness, Comparing Cerebral injury vs. Normal imaging<sup>a</sup>**

(N=15,578)		
Risk Factor	aOR <sup>b</sup> (95% CI)	p-value
Cerebral Injury, with Severe ROP present	3.47 (2.20-5.49)	<0.0001
Cerebral Injury, with Severe ROP absent	10.8 (6.11-19.3)	<0.0001
Severe ROP, with Cerebral Injury present	3.41 (2.33-4.98)	<0.0001
Severe ROP, with Cerebral Injury absent	10.6 (5.00-22.6)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.01
<b>Both Cerebral Injury and Severe ROP vs. Neither<sup>c</sup></b>		
	36.9 (18.7-72.9)	<0.0001

Abbreviation: ROP, Retinopathy of Prematurity.

<sup>a</sup> Infants without normal imaging and without cerebral injury (N=4285) are excluded.

<sup>b</sup> The adjusted odds ratios and p-values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, and center as a cluster effect.

<sup>c</sup> The adjusted odds ratio and p-value for Both cerebral injury and severe ROP vs. Neither is from the same logistic regression model but using different reference levels for the two risk factors, assessing Cerebral injury and Severe ROP as a 4-level variable (Cerebral injury only, Severe ROP only, Both, Neither) with no interaction term.

**eTable 7. Risk Factors for Blindness, Cerebral Injury vs. Normal Imaging**

(N=15,578)	
Risk Factor	Blind
Cerebral Injury	133/4274 (3.1%)
Normal imaging	53/11304 (0.5%)
Severe ROP	122/3544 (3.4%)
No Severe ROP	64/12034 (0.5%)
Cerebral Injury only	47/2836 (1.7%)
Severe ROP only	36/2106 (1.7%)
Both	86/1438 (6.0%)
Neither	17/9198 (0.2%)
If Severe ROP:	N=3544
Cerebral Injury	86/1438 (6.0%)
No Cerebral Injury	36/2106 (1.7%)
If No Severe ROP:	N=12034
Cerebral Injury	47/2836 (1.7%)
No Cerebral Injury	17/9198 (0.2%)
If Cerebral Injury:	N=4274
Severe ROP	86/1438 (6.0%)
No Severe ROP	47/2836 (1.7%)
If Normal imaging:	N=11304
Severe ROP	36/2106 (1.7%)
No Severe ROP	17/9198 (0.2%)

Abbreviation: ROP, Retinopathy of Prematurity.

**eTable 8. Adjusted Odds Ratios (aOR) and 95% Confidence Interval for Blindness, with Blood/Echodensity in Parenchyma not Included in Cerebral Injury Definition**

Risk Factor	aOR <sup>a</sup> (95% CI)	p-value
Cerebral Injury, with Severe ROP present	3.73 (2.40-5.79)	<0.0001
Cerebral Injury, with Severe ROP absent	8.97 (5.71-14.1)	<0.0001
Severe ROP, with Cerebral Injury present	3.35 (2.26-4.97)	<0.0001
Severe ROP, with Cerebral Injury absent	8.06 (4.50-14.4)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.01
<b>Both Cerebral Injury and Severe ROP vs. Neither<sup>b</sup></b>		
	30.1 (16.8-53.6)	<0.0001

Abbreviation: ROP, Retinopathy of Prematurity.

<sup>a</sup> The adjusted odds ratios and p-values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, and center as a cluster effect. Additionally, the following variables were removed during backward stepwise selection: maternal public insurance, gestational age, birth year, antenatal steroids, Hispanic ethnicity, maternal hypertension, and maternal insulin-dependent diabetes.

<sup>b</sup> The adjusted odds ratio and p-value for Both cerebral injury and severe ROP vs. Neither is from the same logistic regression model but using different reference levels for the two risk factors, assessing Cerebral injury and Severe ROP as a 4-level variable (Cerebral injury only, Severe ROP only, Both, Neither) with no interaction term.



**eTable 9. Risk Factors for Blindness, with Blood/Echodensity in Parenchyma not Included in Cerebral Injury Definition**

<b>Risk Factor</b>	<b>Blind</b>
Cerebral Injury	133/4074 (3.3%)
No Cerebral Injury	80/15789 (0.5%)
Severe ROP	139/4568 (3.0%)
No Severe ROP	74/15295 (0.5%)
Cerebral Injury only	47/2687 (1.7%)
Severe ROP only	53/3181 (1.7%)
Both	86/1387 (6.2%)
Neither	27/12608 (0.2%)
If Severe ROP:	N=4568
Cerebral Injury	86/1387 (6.2%)
No Cerebral Injury	53/3181 (1.7%)
If No Severe ROP:	N=15295
Cerebral Injury	47/2687 (1.7%)
No Cerebral Injury	27/12608 (0.2%)
If Cerebral Injury:	N=4074
Severe ROP	86/1387 (6.2%)
No Severe ROP	47/2687 (1.7%)
If No Cerebral Injury:	N=15789
Severe ROP	53/3181 (1.7%)
No Severe ROP	27/12608 (0.2%)

Abbreviation: ROP, Retinopathy of Prematurity.